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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,995	CHARI, RAVI V. J.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *93-120 and 144-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93-120 and 144-151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 120 has been amended. Claims 121-143 have been canceled. Claims 144-151 have been added. Claims 93-120 and 144-151 are pending and under consideration. After review of the prosecution history, it is noted that the elected invention of a composition and kit had the further requirement of an election of species of a chemotherapeutic agent. Applicant elected paclitaxel (synonymous with taxol) as the chemotherapeutic agent along with the species of maytansinoid as an anti-mitotic agent, and the monoclonal antibody or a fragment thereof derived from N901 as the cell-binding agent in the paper filed February 14, 2002,. Accordingly, the pending claims will be examined to the extent that they read on the administration of paclitaxel as a chemotherapeutic agent.

2. Sections of Title 35, U.S. Code not found in this action can be found in a previous Office action.

3. The rejection of claim 120 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 is drawn in part to a synergistic combination of taxol and at least one immunoconjugate of maytansinoid conjugated to a monoclonal antibody which binds to an antigen expressed by the cancer cell. The specification and claims as filed provide support only for the combination of huN901-DM1/paclitaxel, or huC242-DM1/paclitaxel for eliciting a synergistic therapeutic effect (examples 2 and 6, pages 33 and 37). Without a specific description of a genus of antibodies which exert a synergistic therapeutic effect when administered with taxol, one of skill in the art would not assume that the generic combination of antibodies with taxol would exhibit a synergistic effect. Claim 120 is therefore rejected for broadening the scope of the invention as originally filed.

4. Applicant argues that the specification asserts that "The present invention is based on the discover that the use of at least one chemotherapeutic agent and at least one immunoconjugate produces unexpectedly superior results in the treatment of cancer". This has been considered but not found persuasive. "unexpectedly superior results" is not the same as "synergistic". A superior result could be attained by the additive effect of each chemotherapeutic agent or the administration of an agent and an immunoconjugate which obliterates some of the toxic effect of the agent or immunoconjugate. A synergist effect by definition would be a result that was more than the additive effect of the chemotherapeutic agent and the immunoconjugate. It is noted that the specification only provides two examples of synergistic-acting combinations, both of which rely on the specific immunoconjugate with paclitaxel. One of skill in the art would reasonably conclude upon reading of the instant application, that the combinations of huN901-DM1/paclitaxel, or huC242-DM1/paclitaxel are the preferred embodiments of the instant invention, but that other combinations, although efficacious, would not be synergistic. Applicant has provided a dictionary definition of "synergism" that was identical to the examiners definition.

5. The rejection of claims 93-97, 99, 102-110, 112, 115-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegall et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A185) in view of Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131) is maintained for reasons o record.

Claim 93 is drawn to a pharmaceutical composition comprising a therapeutically effective amount of at least one chemotherapeutic agent and at least one immunoconjugate; wherein the immunoconjugate comprises at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof and wherein the monoclonal antibody or fragment thereof bind to an antigen expressed by a cancer cell. Claims 94-97 embody the composition of claim 93, wherein the chetoherpae6uic agent is paclitaxel. Claim 99 embodies the composition of claim 93 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claims 102-104

specify the structure of a modified maytansinoid having a "thiol handle" for conjugation to an antibody.

Claim 106 is drawn to a kit comprising a therapeutically effective amount of at least one chemotherapeutic agent and at least one immunoconjugate; wherein the immunoconjugate comprises at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof and wherein the monoclonal antibody or fragment thereof bind to an antigen expressed by a cancer cell. Claims 107-110 embody the kit of claim 106 wherein the chemotherapeutic agent is paclitaxel. Claim 112 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claims 115-117 specify the structure of the maytansinoid having a "thiol handle" for conjugation to an antibody. Claim 118 and 119 specify that the kit of claim 106 comprises the immunoconjugate and chemotherapeutic agent are in the form of separate compositions, and compositions within the kit, respectively.

Siegall et al teach that combination therapy with BR96 sFv-PE40 and the chemotherapeutic agent paclitaxel were found to have greater antitumor effects in rodents carrying large tumor burdens than either agent alone. The immunotoxin of Siegall et al comprised a single chain antibody which binds to the LeY antigen expressed by human carcinomas, thus fulfilling the specific embodiment of an antibody or fragment thereof that binds to an antigen expressed by a cancer cell, and the specific embodiment of a fragment of a monoclonal antibody that is Fv. Siegall et al teach an immunotoxin conjugated to PE40, which is a modified from of pseudomonas endotoxin . Siegall et al do not teach a BR96 sVf-maytansinoid.

Chari et al teach the chemical synthesis of the structures of claims 102-105, 115-117 and 120. Chari et al teach the conjugation of an antibody which specifically binds to the neu antigen on tumor cells tumor cells, TA.1 (page 128, first column, lines 17-22, Figure 2, page 129, figure 3). Chari et al teach that the high specific activity of maytansinoid conjugate toward tumor cell lines in comparison with low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (page 130, first column, lines 5-9). Chari et al teach the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in

the fact that protein toxins act catalytically rather than stoichiometrically (page 127, first column, lines 16-22 under the heading of "Introduction").

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute maytansinoid for the PE40 toxin in the combination of BR96-sFv-PE40 taught by Siegall et all. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chari et al on the catalytic action of protein toxins versus the stoichiometric action of anticancer drugs. One of skill in the art would recognize that both PE40 and maytansin are protein toxins which act catalytically when internalized by a cell, thus one of skill in the art would expect that a BR96-sFv-maytansinoid immunotoxin would have a similar therapeutic potential as the Br96-sFc-Pe40 immunotoxin.

6. The rejection of claims 93-97, 99, 101-110, 112 and 114-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action) in view of the abstract of Iwasaki et al (Yakugaku Zasshi, 1998, Vol. 118, pp. 111-126) and Pegram et al (Oncogene, 1999, Vol. 18, pp. 2241-2251) and Watson et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A2997) and (Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) is maintained for reasons of record. Newly added claims 144, 146, 148 and 150 are rejected for the same reasons of record. Claim 101 embodies the pharmaceutical composition of claim 93 wherein the monoclonal antibody or fragment thereof is humanized C242. Claim 114 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is humanized C242. Claim 144 is drawn to a pharmaceutical composition comprising paclitaxel and a humanized monoclonal antibody selected from the group consisting of N901 and C242. Claim 146 is drawn to a kit comprising a therapeutically effective amount of paclitaxel and a humanized monoclonal antibody selected from the group consisting of N901 and C242. Claim 148 is drawn to a pharmaceutical composition comprising paclitaxel and a humanized monoclonal antibody or a fragment thereof that binds to an antigen expressed by small cell lung cancer, a non-

small cell lung cancer or a colorectal cell. Claim 150 is drawn to a kit comprising a therapeutically effective amount of paclitaxel and a humanized monoclonal antibody or a fragment thereof that binds to an antigen expressed by small cell lung cancer, a non-small cell lung cancer or a colorectal cell.

Liu et al teach a C242-DM1 conjugate (pages 170 to 171 in sections 2 and 3 Liu et al teach that the C242 maytansinoid conjugate killed antigen positive COLO 205 cells in vitro and caused decreased tumor burden of transplanted human colon cancer xenographs in immunodeficient mice.). Liu et al teach that a reason for lack of clinical efficacy with antibody drug conjugates can be attributed to insufficient accumulation of drug both intratumorally and intracellularly to kill large numbers of tumor cells (page 169, second column, last paragraph). Liu et al teach that this phenomenon can be attributed to the limited expression of target antigens on tumor cells which restricts the amount of drug delivered (page 170, first column, line 8-10) as well as lack of cytotoxic potency and inefficient release of the active drug from the antibody inside the cell (page 170, first column, lines 2-7 and lines 14-15). Liu et al teach that maytansinoids effect cell killing by interfering with the formation of microtubules and depolymerization of already existing microtubules (page 170, column 1, lines 23-26). Liu et al do not teach the administration of the C242-Dm1 conjugate with taxol.

The abstract of Iwasaki et al teaches the existence of a distinct rhizoxin/maytansinoid binding site within tubulin which partially overlaps the vinblastine binding site (VLB). The abstract teaches that taxol binds to tubulin at a site other than the colchicine site (CLC) or the vinblastine site (VLB) and that taxol is an antitubulin agent which promotes microtubule formation (lines 29-32).

Watson et al teaches that taxol stabilizes microtubules resulting in the arrest of the cells at G2/M. One of skill in the art would conclude that taxol was an anti-mitotic agent as cells were arrested at G2/M and unable to go through mitosis and enter G1.
Pegram et al teach that the interaction between two drugs may result in an additive effect, a synergistic effect, or an antagonistic effect. Pegram et al point out that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in an antagonistic interaction (page 2242, first column, lines 6-9).

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of marine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the marine antibodies (pages 97-98, bridging paragraph).

Schlom teaches the advantages of single chain antibodies over the parent marine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30). One of skill in the art would be motivated to make the humanized version of the C242 antibody for administration of the maytansinoid immunoconjugate to humans. One of skill in the art would also be motivated to make the scFv fragment of the C242 for administration to humans based on the teachings of Liu et al regarding the poor penetration of immunoconjugates into tumor (page 170, first column, lines 11-12) and the teachings of Schlom on the enhanced ability of scFv to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments. One of skill in the art would logically be motivated to make a reagent which would maximize the delivery of the maytansinoid to the tumor. By making a humanized C242 antibody, the lack of a HAMA response will allow more of the antibody to reach the tumor on subsequent doses. By making a scFv from C242 the smaller fragment will have a decreased HAMA response and better ability to penetrate into the tumor.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a humanized C242-DM1 immunoconjugate with taxol or the administration of scFv of C242-DM1 with taxol for the treatment of colorectal tumors. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of

Liu et al on the limited expression of target antigens on tumor cells which restricts the amount of drug delivered as an impediment to the clinical efficacy of immunoconjugates and the teachings of Liu et al on the antitubulin mode of action of maytansinoid, the delivered drug. One of skill in the art would realize that tumors which are lacking the CanAg to which the C242 antibody binds will not internalize the immunoconjugate and thus will not be exposed to enough anti-tubulin inhibiting drug within the cytoplasm. In addition the teachings of Pegram et al point out that administration of two drugs could result in antagonism if the two drugs were targeted to the same molecular mechanism. The teachings of Liu et al point out that maytansinoids kill cells by interfering with the formation of microtubules and depolymerization of already existing microtubules. The teachings of the abstract of Iwasaki et al point out that taxol stabilizes microtubulin and does not bind to the same site on tubulin as vinblastine. The teachings of Watson et al point out that taxol arrests cells in G2/M due t the stabilization of microtubulin.
One of skill in the art would be motivated to combine the C242-DM1 immunotoxin with taxol in order to exert a cytotoxic effect on cells which do not express enough of the CanAg targeted by the C242 antibody to result in accumulation of a sufficient amount of the maytansinoid to be cytotoxic. One of skill in the art would recognize that in the cells which express enough of the CanAg to internalize the C242-Dm1 immunoconjugate to the extent that sufficient Maytansinoid will accumulate and exert a cytotoxic effect, taxol will not compete with maytansinoid in the binding of tubulin because taxol and maytansinoid bind to different sites on tubulin, and thus, the administration of taxol in combination with C242-DM1 would not result in an antagonistic effect on said cells. Because the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect.

7. Claims 93-97, 99, 101-110, 112, 114-119 and 144-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 93-97, 99, 101-110, 112, 114-119, 144, 146, 148 and 150 above, and further in view of Chari et al.

Chari et al teach the chemical synthesis of the structures of claims 102-105, 115-117, 120, 145, 147, 149 and 150. Chari et al teach the conjugation of an antibody which specifically binds to the neu antigen on tumor cells tumor cells, TA.1 (page 128, first column, lines 17-22, Figure 2, page 129, figure 3). Chari et al teach that the high specific activity of maytansinoid conjugate toward tumor cell lines in comparison with low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (page 130, first column, lines 5-9). Chari et al teach the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in the fact that protein toxins act catalytically rather than stoichiometrically (page 127, first column, lines 16-22 under the heading of "Introduction").

It would have been prima facie obvious to make the immunoconjugates comprising the maytansoinoids synthesized by Chari. One of skill in the art would have been motivated to do so by the teachings of Chari on the high therapeutic index afforded by Maytansinoid toxins relative to chemotherapeutic agents.

8. The rejection of claims 93-98, 100-111, 113, 115-119 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Guchelaar et al (Clinical Oncology, 1994, Vol. 6, pp. 40-48) in view of Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190) and the abstract of Lynch et al (Journal of Clinical oncology, 1997, Vol. 15, pp. 723-734) and Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action) and the abstract of Iwasaki et al (Yakugaku Zasshi, 1998, Vol. 118, pp. 111-126) and Pegram et al (Oncogene, 1999, Vol. 18, pp. 2241-2251) is maintained for reasons of record.

The specific embodiments of claims 93-97, 101-110, 115-119 are set forth above. Claim 98 embodies the composition of claim 93 wherein the monoclonal antibody binds to a CD5 antigen. Claim 100 embodies the composition of claim 93 wherein the antibody or a fragment thereof is humanized N901. Claim 111 embodies the kit of claim 106 wherein the monoclonal antibody or a fragment thereof binds to CD56. Claim 113

embodies the kit of claim 106 wherein the monoclonal antibody or a fragment thereof is humanized N901.

The abstract of Guchelar et al teaches that taxol shows a 37% response rate in the treatment of advanced small cell lung cancer. The abstract does not teach the administration of the humanized N901-DM1 conjugate.
Liu et al (AACR) teach that the administration an immunotoxin conjugate comprising the humanized N901 antibody and maytansinoid (DM1) was effective at killing human small cell lung xenographs in immunodeficient mice. The abstract of Lynch et al teaches that N901 is a monoclonal antibody that binds to the CD56 neural cell adhesion molecule of NCAM., thus fulfilling the specific embodiment of claims 98and 11 specifying binding to CD56. Liu et al do not teach the administration of taxol

The abstract of Watson et al teaches that taxol stabilizes microtubules resulting in the arrest of the cells at G2/M. One of skill in the art would conclude that taxol was an anti-mitotic agent as cells were arrested at G2/M and unable to go through mitosis and enter G1.

The abstract of Iwasaki et al teaches the existence of a distinct rhizoxin/maytansinoid binding site within tubulin which partially overlaps the vinblastine binding site (VLB). The abstract teaches that taxol binds to tubulin at a site other than the vinblastine site (VLB) and that taxol is an antitubulin agent which promotes microtubule formation (lines 29-32).

Liu et al(EOID) teach that maytansinoids kill cells by interfering with the formation of microtubules and depolymerization of already existing microtubules (page 170, first column, lines 2326). Liu et al teach the modified structure of maytansinoid allowing for the attachment of a monoclonal antibody by means of the thiol "handle" (figure1, structure 2).

Pegram et al teach that the interaction between two drugs may result in an additive effect, a synergistic effect, or an antagonistic effect. Pegram et al point out that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in an antagonistic interaction (page 2242, first column, lines 6-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a humanized N901-DM1 immunoconjugate with taxol for the treatment of small cell lung carcinoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Guchelaar et al who indicate that the administration of taxol alone has some efficacy in the treatment of advanced small cell lung carcinoma; the teachings of Liu et al (AACR) on the efficacy of the N901-DM1 immunoconjugate against human small cell lung cancer xenographs and the teachings of the abstract of Iwasaki et al and Liu (EOID) on the different binding sites of maytansinoid and taxol on tubulin, and the teachings of Liu (EOID) and the abstract of Watson on the different effects exerted on tubulin by taxol and maytansinoid in light of the teachings of Pergram on the avoidance of targeting the same molecular mechanism by the administration of two drugs wherein the resulting in the effect would be antagonistic. In the instant case the binding of tubulin by taxol would not result in an antagonistic competition with maytansinoid because taxol and maytansinoid bind tubulin at separate locations. Because the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect.

9. The rejections of claims 93-113 and 115-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Guchelaar et al Clinical Oncology, 1994, Vol. 6, pp. 40-48) and Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190) and Liu (Expert opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172 and the abstract of Iwasaki et al (Yakugaku Zasshi, 1998, Vol. 118, pp. 111-126) and Pegram et al (Oncogene, 1999, Vol. 18, pp. 2241-2251) as applied to claims 93-98, 100-111, 113, 115-119 above, and further in view of Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) is maintained for reasons of record. The specific embodiments of the claims and the teachings of the combined references which render obvious claims 93-98, 100-111, 113, 115-119 are set forth above. Claim 99 embodies the composition of claim 93

wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claim 112 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2.
Neither of Guchelaar et al, Liu et al (AACR), Liu et al (EOID), the abstract of Iwasaki et al nor Pegram et al teach the administration of fragments of N901.

Liu et al (EOID) teach that a lack of clinical efficacy of immunoconjugates can be attributed to poor penetration of said immunoconjugates into tumors (page 170, first column, lines 11-12).

Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, and increased penetration into tumor masses, (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine taxol with scFv conjugated to DM1 in place of N901-DM1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Liu et al regarding the lack of tumor penetration as a reasons for reduced toxicity of immunoconjugates in vivo, and the teachings of Schlom et al regarding the administration of scFv in place of whole antibodies for increasing tumor penetration in vivo.

10. The rejection of claims 93-97, 99, 102-110, 112, 115-119 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,208,020 in view of Siegall et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A185) and Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131) is maintained for reasons of record.

The specific embodiments of the claims are set forth above.

Siegall et al teach that combination therapy with BR96 sFv-PE40 and the chemotherapeutic agent paclitaxel were found to have greater antitumor effects in rodents

carrying large tumor burdens than either agent alone. The immunotoxin of Siegall et al comprised a single chain antibody which binds to the LeY antigen expressed by human carcinomas, thus fulfilling the specific embodiment of an antibody or fragment thereof that binds to an antigen expressed by a cancer cell, and the specific embodiment of a fragment of a monoclonal antibody that is Fv. Siegall et al teach an immunotoxin conjugated to PE40, which is a modified from of pseudomonas endotoxin . Siegall et al do not teach a BR96 sVf-maytansinoid.

Chari et al (Cancer Research) teach the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in the fact that protein toxins act catalytically rather than stoichiometrically (page 127, first column, lines 16-22 under the heading of "Introduction").

Claims 1-6 of the '020 patent are drawn in part to cytotoxic agents comprising one or more maytansinoids conjugated to a monoclonal antibody or fragment thereof via a disulfide bridge at the C3 position of said maytansinoids and wherein said monoclonal antibody or fragment thereof is selective for tumor cell antigens. Claims 7-12 are drawn to pharmaceutical composition comprising maytansinoids conjugated to a monoclonal antibody or fragment thereof via a disulfide bridge at the C3 position of said maytansinoids and wherein said monoclonal antibody or fragment thereof is selective for tumor cell antigens. Conjugation of the monoclonal antibody to the maytansinoid via the C3 position of maytansinoid is the same as the structures of instant claims 102,-105 and 115-117.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute maytansinoid for the PE40 toxin in the combination of BR96-sFv-PE40 taught by Siegall et all. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chari et al (Cancer Research) on the catalytic action of protein toxins versus the stoichiometric action of anticancer drugs. One of skill in the art would recognize that both PE40 and maytansin are protein toxins which would act catalytically within the cell, thus one of skill in the art would expect that a BR96-sFv-maytansinoid immunotoxin would have a similar therapeutic potential as the Br96-sFc-Pe40 immunotoxin.

Thus, the instant claims 93-97, 99, 102-110, 112, 115-119 would have been obvious over, the reference claim(s) 1-12 because it would be obvious to combine the reference claims with the teachings to Siegall et al and Chari et al (Cancer Research) for the reasons set forth above.

11. Applicant has previously argued that after a reading of Liu et al on the administration of C242-DM1 one of skill in the art would be motivated to use the immunoconjugate as a single agent and thus the disclosure of Liu et al actually teaches away from the instant invention. This has been considered but not found persuasive. the teachings of Liu et al are directed to the decrease in tumor burden of a human xenograph in immunodeficient mice. Liu et al teaches that some of the reasons why clinical efficacy has not been realized for immunoconjugates is due to the lack of expression of the target antigen on the tumor cell and the lack of penetration of the targeting antibody into the tumor mass both of which would result in lack of accumulation of the toxin within the targeted tumor cells. The experiment with transplanted tumor in mice involve the transplantation of tumor cell lines. Tumors growth in situ differ from tumor cell lines in three dimensional organization and in molecular heterogeneity. Schlom (cited above) teaches the parameters for monoclonal antibody based therapy which include number of antigen molecules per cell, number of cells expressing the reactive antigen in the tumor mass, the size and degree of vascularization of the tumor mass (page 98, Table 6.2). Schlom also teaches that "virtually every property of a tumor cell population has been shown to demonstrate some degree of heterogeneity or modulation either between different tumor masses or among cells of a given tumor mass...expression of some tumor associated antigens is no exception" (page 109, second column, lines 1-10 under the heading "Up Regulation of Target Antigens"). Thus, given the teachings of Liu et al regarding the lack of clinical efficacy for immunoconjugates due to the lack of effective delivery of the conjugated toxin to a large number of tumor cells one of skill in the art would not expect, based on a transplanted tumor animal model, that the C242-DM1 would be effective as a single agent for the treatment of colorectal cancers because the transplanted xenograph is a transplanted tumor cell line which differs from a tumor in situ

in that a tumor in situ is expected to exhibit antigen heterogeneity as taught by Schlom and Liu et al.

12. Applicant argues that the teachings of Siegall et al "are "wholly unrelated" to the instant invention. Siegall et al teaches an immunoconjugate which binds to a cancer antigen. The claims are broadly drawn to the immunoconjugate binding a generic "cancer antigen". Therefore Siegall et al is germane to the instant invention.

13. Applicant argues that the initial rejection was faulty because the examine stated that maytansinoid acts in a catalytic fashion. Applicant argues that this is not true as maytansinoid acts by binding to tubulin, not in a catalytic fashion. Applicant argues that all the 103 rejections are therefore faulty because they rely on the combination of Siegall et al and Chari et al However, Chari et al, (Chari is an instant inventor) teach that maytansinoid acts catalytically and therefore is superior to anticancer drugs (page 127, first column, lines 16-22 under the heading of "Introduction"). Whether or not this statement of Chari et al was later proved false, one of skill in the art would have been motivated by the teachings of Chari et al to use maytansinoid as part of an immunoconjugate. Further, Chari et al teach that maytansinoid possesses a very high therapeutic index. One of skill in the art would be motivated to use an immunotoxin which binds to an internalizing cancer antigen wherein said immunotoxin comprises maytansinoid in order to take advantage of the ability of maytansinoid to exert a toxic effect on a cell once internalized irregardless of what the molecular basis of the maytansinoid activity was attributed to.

14. Applicant argues against the rejections under 103(a) on pages 6-12, sections 8-10, of the previous Office action, and the obvious-type double patenting rejection, stating that the combinations would not be expected to be synergistic. Applicant has provided an entire tabulation of data regarding synergistic combination of immunoconjugates targeting CD56 and CanAg wherein the toxin portion of the immunoconjugate is maytansinoid. The examiner agrees that said combinations would not be expected to be

synergistic: that is why claim 120 was not included with the instant rejections. However, the claims at issue here are drawn to pharmaceutical compositions and kits. The motivation for combining the individual references rests on the fact that the combination would be expected to be "non-antagonistic" and therefore additive to some degree. One of skill in the art would be motivated to make such compositions as they would be expected to afford a more efficacious therapy than the single agents alone. Applicant argues that the Declaration of Dr. Blattler stating that "one of skill in the art would have expected that huN901 and huC242 in Examples 2-7 could have been substituted with other monoclonal antibodies that bind to antigens expressed on cancer cells and that the same or substantially the same greater than additive results would have been achieved". This has been considered but not found persuasive. Because synergism is an unexpected result, it would not be obvious that immunoconjugates targeting other cancer antigens in combination with other drugs would expected to be synergistic and further this is not relevant to the instant claims which do not require s synergistic effect between the chemotherapeutic agent and the immunoconjugate.

15. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicant arguments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/9/2004